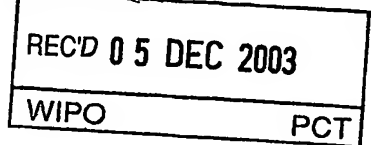




PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH
RULE 17.1(a) OR (b)

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ



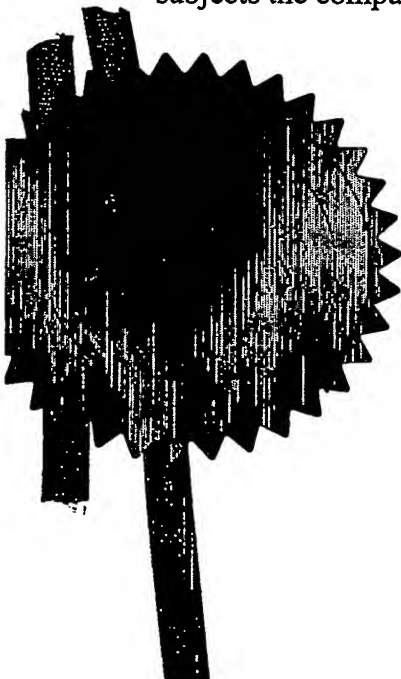
PCT/US03/33207

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation and Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the international application filed on 18 October 2002 under the Patent Cooperation Treaty at the UK Receiving Office. The application was allocated the number PCT/GB2002/004735.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or the inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.



Signed

W Taylor

Date:

6 November 2003

BEST AVAILABLE COPY

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

PCT/GB 2002 / 004735

International Application No.

18 OCTOBER 2002

International Filing Date

United Kingdom Patent Office
PCT International Application

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) WPP86785

Box No. I TITLE OF INVENTION	
USE OF ANTITUMOURAL COMPOUNDS IN CANCER THERAPY	
Box No. II APPLICANT <input type="checkbox"/> This person is also inventor	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)	
Pharma Mar, S.A. Calle de la Calera 3 Poligono Industrial de Tres Cantos Tres Cantos, Madrid E-28760 Spain	
State (that is, country) of nationality: ES	
State (that is, country) of residence: ES	
This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input checked="" type="checkbox"/> all designated States except the United States of America <input type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box	
Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)	
Jimeno, José Pharma Mar, S.A. Calle de la Calera 3 Poligono Industrial de Tres Cantos Tres Cantos, Madrid E-28760 Spain	
State (that is, country) of nationality: ES	
State (that is, country) of residence: ES	
This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box	
<input checked="" type="checkbox"/> Further applicants and/or (further) inventors are indicated on a continuation sheet.	
Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE	
The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: <input checked="" type="checkbox"/> agent <input type="checkbox"/> common representative	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)	
Ruffles, Graham Keith Marks & Clerk 57-60 Lincoln's Inn Fields London WC2A 3LS United Kingdom	
Telephone No. 020 7400 3000	
Facsimile No. 020 7404 4910	
Teleprinter No. 25311 EMANDC G	
Agent's registration No. with the Office	
<input type="checkbox"/> Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.	

Sheet No. ...2...

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)			
If none of the following sub-boxes is used, this sheet should not be included in the request.			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) López Lázaro, Luis Pharma Mar, S.A. Calle de la Calera 3 Poligono Industrial de Tres Cantos Tres Cantos, Madrid E-28760 Spain		This person is: <input type="checkbox"/> applicant only <input checked="" type="checkbox"/> applicant and inventor <input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office	
State (that is, country) of nationality: ES		State (that is, country) of residence: ES	
This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) Ruiz Casado, Ana Pharma Mar, S.A. Calle de la Calera 3 Poligono Industrial de Tres Cantos Tres Cantos, Madrid E-28760 Spain		This person is: <input type="checkbox"/> applicant only <input checked="" type="checkbox"/> applicant and inventor <input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office	
State (that is, country) of nationality: ES		State (that is, country) of residence: ES	
This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) Izquierdo, Miguel Angel Pharma Mar, S.A. Calle de la Calera 3 Poligono Industrial de Tres Cantos Tres Cantos, Madrid E-28760 Spain		This person is: <input type="checkbox"/> applicant only <input checked="" type="checkbox"/> applicant and inventor <input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office	
State (that is, country) of nationality: ES		State (that is, country) of residence: ES	
This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) Paz-Ares, Luis Hospital doce de Octubre carretera de Andalucía Km. 5,400 Madrid 28041 Spain		This person is: <input type="checkbox"/> applicant only <input checked="" type="checkbox"/> applicant and inventor <input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office	
State (that is, country) of nationality: ES		State (that is, country) of residence: ES	
This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box			
<input checked="" type="checkbox"/> Further applicants and/or (further) inventors are indicated on another continuation sheet.			

Sheet No. ...3...

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) Ruffles, Graham Keith 57-60 Lincoln's Inn Fields London WC2A 3LS United Kingdom	This person is: <input checked="" type="checkbox"/> applicant only <input type="checkbox"/> applicant and inventor <input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)
	Applicant's registration No. with the Office

State (that is, country) of nationality: GB	State (that is, country) of residence: GB
This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input type="checkbox"/> the United States of America only <input checked="" type="checkbox"/> the States indicated in the Supplemental Box	

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) Trigo, Jose Manuel Hospital Vall D'Hebron Pg. Vall d'Hebron 119-129 Barcelona 08035 Spain	This person is: <input type="checkbox"/> applicant only <input checked="" type="checkbox"/> applicant and inventor <input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)
	Applicant's registration No. with the Office

State (that is, country) of nationality: ES	State (that is, country) of residence: ES
This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box	

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) Schellens, Jan The Netherlands Cancer Institute Plesmanlaan 121 Amsterdam 1066 CX The Netherlands	This person is: <input type="checkbox"/> applicant only <input checked="" type="checkbox"/> applicant and inventor <input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)
	Applicant's registration No. with the Office

State (that is, country) of nationality: NL	State (that is, country) of residence: NL
This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box	

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) 	This person is: <input type="checkbox"/> applicant only <input type="checkbox"/> applicant and inventor <input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)
	Applicant's registration No. with the Office

State (that is, country) of nationality:	State (that is, country) of residence:
This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box	

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Sheet No. ...4...

No. V DESIGNATION OF STATES

Mark the applicable check-boxes below; at least one must be marked.

The following designations are hereby made under Rule 4.9(a):

Regional Patent

- ☒ AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT (if other kind of protection or treatment desired, specify on dotted line)
- ☒ EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP European Patent: AT Austria, BE Belgium, BG Bulgaria, CH & LI Switzerland and Liechtenstein, CY Cyprus, CZ Czech Republic, DE Germany, DK Denmark, EE Estonia, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, SK Slovakia, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | | |
|---|--|--|
| <input checked="" type="checkbox"/> AE United Arab Emirates | <input checked="" type="checkbox"/> GM Gambia | <input checked="" type="checkbox"/> NZ New Zealand |
| <input checked="" type="checkbox"/> AG Antigua and Barbuda | <input checked="" type="checkbox"/> HR Croatia | <input checked="" type="checkbox"/> OM Oman |
| <input checked="" type="checkbox"/> AL Albania | <input checked="" type="checkbox"/> HU Hungary | <input checked="" type="checkbox"/> PH Philippines |
| <input checked="" type="checkbox"/> AM Armenia | <input checked="" type="checkbox"/> ID Indonesia | <input checked="" type="checkbox"/> PL Poland |
| <input checked="" type="checkbox"/> AT Austria | <input checked="" type="checkbox"/> IL Israel | <input checked="" type="checkbox"/> PT Portugal |
| <input checked="" type="checkbox"/> AU Australia | <input checked="" type="checkbox"/> IN India | <input checked="" type="checkbox"/> RO Romania |
| <input checked="" type="checkbox"/> AZ Azerbaijan | <input checked="" type="checkbox"/> IS Iceland | <input checked="" type="checkbox"/> RU Russian Federation |
| <input checked="" type="checkbox"/> BA Bosnia and Herzegovina | <input checked="" type="checkbox"/> JP Japan | |
| <input checked="" type="checkbox"/> BB Barbados | <input checked="" type="checkbox"/> KE Kenya | <input checked="" type="checkbox"/> SD Sudan |
| <input checked="" type="checkbox"/> BG Bulgaria | <input checked="" type="checkbox"/> KG Kyrgyzstan | <input checked="" type="checkbox"/> SE Sweden |
| <input checked="" type="checkbox"/> BR Brazil | <input checked="" type="checkbox"/> KP Democratic People's Republic of Korea | <input checked="" type="checkbox"/> SG Singapore |
| <input checked="" type="checkbox"/> BY Belarus | <input checked="" type="checkbox"/> KR Republic of Korea | <input checked="" type="checkbox"/> SI Slovenia |
| <input checked="" type="checkbox"/> BZ Belize | <input checked="" type="checkbox"/> KZ Kazakhstan | <input checked="" type="checkbox"/> SK Slovakia |
| <input checked="" type="checkbox"/> CA Canada | <input checked="" type="checkbox"/> LC Saint Lucia | <input checked="" type="checkbox"/> SL Sierra Leone |
| <input checked="" type="checkbox"/> CH & LI Switzerland and Liechtenstein | <input checked="" type="checkbox"/> LK Sri Lanka | <input checked="" type="checkbox"/> TJ Tajikistan |
| <input checked="" type="checkbox"/> CN China | <input checked="" type="checkbox"/> LR Liberia | <input checked="" type="checkbox"/> TM Turkmenistan |
| <input checked="" type="checkbox"/> CO Colombia | <input checked="" type="checkbox"/> LS Lesotho | <input checked="" type="checkbox"/> TN Tunisia |
| <input checked="" type="checkbox"/> CR Costa Rica | <input checked="" type="checkbox"/> LT Lithuania | <input checked="" type="checkbox"/> TR Turkey |
| <input checked="" type="checkbox"/> CU Cuba | <input checked="" type="checkbox"/> LU Luxembourg | <input checked="" type="checkbox"/> TT Trinidad and Tobago |
| <input checked="" type="checkbox"/> CZ Czech Republic | <input checked="" type="checkbox"/> LV Latvia | |
| <input checked="" type="checkbox"/> DE Germany | <input checked="" type="checkbox"/> MA Morocco | <input checked="" type="checkbox"/> TZ United Republic of Tanzania |
| <input checked="" type="checkbox"/> DK Denmark | <input checked="" type="checkbox"/> MD Republic of Moldova | <input checked="" type="checkbox"/> UA Ukraine |
| <input checked="" type="checkbox"/> DM Dominica | <input checked="" type="checkbox"/> MG Madagascar | <input checked="" type="checkbox"/> UG Uganda |
| <input checked="" type="checkbox"/> DZ Algeria | <input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia | <input checked="" type="checkbox"/> US United States of America |
| <input checked="" type="checkbox"/> EC Ecuador | <input checked="" type="checkbox"/> MN Mongolia | |
| <input checked="" type="checkbox"/> EE Estonia | <input checked="" type="checkbox"/> MW Malawi | <input checked="" type="checkbox"/> UZ Uzbekistan |
| <input checked="" type="checkbox"/> ES Spain | <input checked="" type="checkbox"/> MX Mexico | <input checked="" type="checkbox"/> VN Viet Nam |
| <input checked="" type="checkbox"/> FI Finland | <input checked="" type="checkbox"/> MZ Mozambique | <input checked="" type="checkbox"/> YU Yugoslavia |
| <input checked="" type="checkbox"/> GB United Kingdom | <input checked="" type="checkbox"/> NO Norway | <input checked="" type="checkbox"/> ZA South Africa |
| <input checked="" type="checkbox"/> GD Grenada | | <input checked="" type="checkbox"/> ZM Zambia |
| <input checked="" type="checkbox"/> GE Georgia | | <input checked="" type="checkbox"/> ZW Zimbabwe |
| <input checked="" type="checkbox"/> GH Ghana | | |

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

- ☒ VC St Vincent and the Grenadines ☐ ☐
- ☐ ☐ ☐

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

Supplemental Box

If the Supplemental Box is not used, this sheet should not be included in the request.

1. If, in any of the Boxes, except Boxes Nos. VIII(i) to (v) for which a special continuation box is provided, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:
 - (i) if more than two persons are to be indicated as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;
 - (ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;
 - (iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;
 - (iv) if, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;
 - (v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;
 - (vi) if, in Box No. VI, there are more than five earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.
2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.

Continuation of Box III

Ruffles, Graham Keith is co-applicant for SD (Sudan)
only

Sheet No. ...6...

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application:* regional Office	international application: receiving Office
item (1) 19 October 2001 (19.10.01)	60/348,449	US		
item (2) 31 October 2001 (31.10.01)	PCT/GB01/04821	GB		
item (3) 26 September 2002 (26.09.02)	0222409.5	GB		
item (4)				
item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office) identified above as:

☐ all items
 ☐ item (1)
 ☒ item (2)
 ☒ item (3)
 ☐ item (4)
 ☐ item (5)
 ☐ other, see Supplemental Box

* Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA /

Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year) Number Country (or regional Office)

Box No. VIII DECLARATIONS


The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):

Number of
declarations

- | | | |
|---|--|---|
| <input type="checkbox"/> Box No. VIII (i) | Declaration as to the identity of the inventor | : |
| <input type="checkbox"/> Box No. VIII (ii) | Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent | : |
| <input type="checkbox"/> Box No. VIII (iii) | Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application | : |
| <input type="checkbox"/> Box No. VIII (iv) | Declaration of inventorship (only for the purposes of the designation of the United States of America) | : |
| <input type="checkbox"/> Box No. VIII (v) | Declaration as to non-prejudicial disclosures or exceptions to lack of novelty | : |

Sheet No. ...7...

Box No. IX CHECK LIST; LANGUAGE OF FILING

<p>This international application contains:</p> <p>(a) the following number of sheets in paper form:</p> <p>request (including declaration sheets) : 7</p> <p>description (excluding sequence listing part) : 30</p> <p>claims : 6</p> <p>abstract : 1</p> <p>drawings : 44</p> <p>Sub-total number of sheets : 44</p> <p>sequence listing part of description (<i>actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below</i>) : 44</p> <p>Total number of sheets : 44</p> <p>(b) sequence listing part of description filed in computer readable form</p> <p>(i) <input type="checkbox"/> only (under Section 801(a)(i))</p> <p>(ii) <input type="checkbox"/> in addition to being filed in paper form (under Section 801(a)(ii))</p> <p>Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained (<i>additional copies to be indicated under item 9(ii), in right column</i>):</p>	<p>This international application is accompanied by the following item(s) (<i>mark the applicable check-boxes below and indicate in right column the number of each item</i>):</p> <p>1. <input checked="" type="checkbox"/> fee calculation sheet : 1</p> <p>2. <input type="checkbox"/> original separate power of attorney : 1</p> <p>3. <input type="checkbox"/> original general power of attorney : 1</p> <p>4. <input checked="" type="checkbox"/> copy of general power of attorney; reference number, if any: : 1</p> <p>5. <input type="checkbox"/> statement explaining lack of signature : 1</p> <p>6. <input type="checkbox"/> priority document(s) identified in Box No. VI as item(s): : 1</p> <p>7. <input type="checkbox"/> translation of international application into (language): : 1</p> <p>8. <input type="checkbox"/> separate indications concerning deposited microorganism or other biological material : 1</p> <p>9. <input type="checkbox"/> sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other)) : 1</p> <p>(i) <input type="checkbox"/> copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application) : 1</p> <p>(ii) <input type="checkbox"/> (<i>only where check-box (b)(i) or (b)(ii) is marked in left column</i>) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter : 1</p> <p>(iii) <input type="checkbox"/> together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column : 1</p> <p>10. <input checked="" type="checkbox"/> other (<i>specify</i>): Form 23/77. x.2 : 1</p>
<p>Figure of the drawings which should accompany the abstract:</p>	<p>Language of filing of the international application: English</p>
<p>Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE</p> <p><i>Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).</i></p>	
<p style="text-align: center;">  Ablewhite. Alan J. <i>for</i> Ruffles, Graham Keith </p>	

For receiving Office use only		
1. Date of actual receipt of the purported international application:	18 OCTOBER 2002 18/10/02	2. Drawings:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:		<input type="checkbox"/> received:
4. Date of timely receipt of the required corrections under PCT Article 11(2):		<input type="checkbox"/> not received:
5. International Searching Authority (if two or more are competent): ISA /	6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid	

For International Bureau use only
Date of receipt of the record copy by the International Bureau:

USE OF ANTITUMOURAL COMPOUNDS IN CANCER THERAPY

FIELD OF THE INVENTION

The present invention relates to the use of kahalalide compounds in the treatment of cancer.

BACKGROUND OF THE INVENTION

Nature is the origin of many effective medicines in oncology, like paclitaxel, adriamycin, etoposide, bleomycin, etc. In recent years the sea has proven to be an invaluable source for compounds displaying original chemical structures and interesting biological activity. Among the cytotoxic compounds from marine origin we can mention the ecteinascidins, didemnins, dolastatins, spissulosines, lamellarins, some of them being developed as antitumoural agents in clinical trials.

The kahalalide compounds are peptides isolated from a Hawaiian herbivorous marine species of mollusc, *Elysia rufescens*. Kahalalides A-F are described in EP 610 078 and Hamman *et al.*, J. Am. Chem. Soc., 1993, 115, 5825-5826.

Kahalalide A-G are described in Hamann, M. *et al.*, J. Org. Chem, 1996, 61, 6594-6600: "Kahalalides: bioactive peptides from a marine mollusk *Elysia rufescens* and its algal diet *Bryopsis* sp.".

Kahalalide H and J are described in Scheuer P.J. *et al.*, J. Nat. Prod. 1997, 60, 562-567: "Two acyclic kahalalides from the sacoglossan mollusk *Elysia rufescens*".

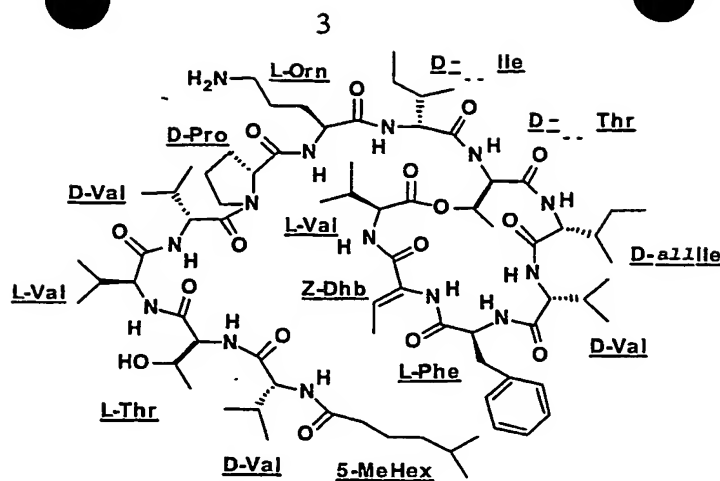
Kahalalide O is described in Scheuer P.J. *et al.*, J. Nat. Prod. 2000, 63(1) 152-4 : A new depsipeptide from the sacoglossan mollusk *Elysia ornata* and the green alga *Bryopsis* species".

For kahalalide K, see Kan, Y. *et al.*, J. Nat. Prod. 1999 62(8) 1169-72 : "Kahalalide K: A new cyclic depsipeptide from the hawaiian green alga *bryopsis* species".

For related reports, see also Goetz *et al.*, Tetrahedron, 1999, 55; 7739-7746: "The absolute stereochemistry of Kahalalide F"; Albericio, F. *et al.* Tetrahedron Letters, 2000, 41, 9765-9769: "Kahalalide B. Synthesis of a natural cyclodepsipeptide"; Becerro *et al.* J. Chem. Ecol. 2001, 27(11), 2287-99: "Chemical defenses of the sarcoglossan mollusk *Elysia rufescens* and its host Alga *bryopsis* sp."

The synthesis and cytotoxic activities of natural and synthetic kahalalide compounds is described in WO 01 58934.

Of the kahalalide compounds, kahalalide F is the most promising because of its antitumoural activity. Kahalalide F now known to have the structure:



Kahalalide F is a tridecapeptide with a ring shape side and a lateral side, containing a fatty acid group connected to the latter. Its activity against in vitro cell cultures of human lung carcinoma A-549 and human colon carcinoma HT-29 were reported in EP 610 078.

WO 02 36145 describes pharmaceutical compositions containing kahalalide F and new uses of this compound in cancer therapy.

See also Beijnen, J.H. *et al.*, Drug Dev. Ind. Pharm. 2001, 27(8) 767-80: "Development of a lyophilized parenteral pharmaceutical formulation of the investigational polypeptide marine anticancer agent kahalalide F"; Beijnen, J.H. *et al.*, Br. J. Clin. Pharmacol. 2002, 53(5), 543: "Bioanalysis of the novel peptide anticancer drug kahalalide F in human plasma by h.p.l.c. under basic conditions coupled with positive turbo-ionspray tandem mass spectrometry"; Beijnen, J.H. *et al.*, PDA J. Pharm. Sci. Technol. 2001, 55(4) 223-9: "In vitro hemolysis and buffer capacity studies with the novel marine anticancer agent Kahalalide F and its reconstitution vehicle cremophor EL/ethanol"; Sparidans R.W. *et al.*, Anticancer Drugs 2001, 12(7) 575-82: "Chemical and enzymatic stability of a cyclic depsipeptide, the novel, marine-derived, anti-cancer agent kahalalide F".

In preclinical studies, kahalalide F has shown significant activity against solid tumour cell lines, and selectivity for, but not restricted to, prostate tumour cells, neuroblastomas, some primary sarcoma lines and tumour cells that overexpress the Her2/neu oncogene. In vitro exposure studies demonstrated that kahalalide F is not schedule dependent. Its mechanism of action is not yet elucidated, in vitro studies have shown activity of kahalalide F to cause cell swelling and ultimately death, see for example Garcia-Rocha M, Bonay P, Avila J., Cancer Lett. 1996 99(1) 43-50: "The antitumoural compound Kahalalide F acts on cell lysosomes".

Preclinical in vivo studies determined that the maximum tolerated dose (MTD) of KF in female mice following a single bolus iv injection was to be 280 µg/kg. Whereas single doses just above the MTD were extremely toxic, with animals exhibiting signs of neurotoxicity followed by death, 280 µg/kg KF could be administered repeatedly, according to a once daily times five schedule, without any apparent evidence of acute toxicity. See Supko, F. *et al.*, Proceedings of the 1999 AACR NCI EORTC International Conference, abstract 315: "Preclinical pharmacology studies with the marine natural product Kahalalide F".

During preclinical studies kahalalide F exhibited low cardiac and skeletal muscle toxicities and also low myelotoxicity. In mice, the main toxicities found were tubular nephrotoxicity and CNS (central nervous system) neurotoxicity, and hints of hepatotoxicity. Therefore the expected toxicities were renal and neurologic with a marked threshold. As mentioned before, whereas MTD had no lethality, doses slightly over MTD showed high lethality.

It is an object of the present invention to provide new, improved forms

of treatment using kahalalide compounds showing clinical benefit.

In particular, it is an object of the invention to provide dosages and schedules of kahalalide compounds that can be used for cancer therapy in humans, avoiding toxicities while maintaining the desired antineoplastic effects.

It is another object of the present invention to provide new uses in cancer therapy for the kahalalide compounds, in particular for kahalalide F.

It is yet another object of the invention to provide new products containing kahalalide compounds, in particular kahalalide F, for administration in the treatment of cancer.

SUMMARY OF THE INVENTION

We have developed a method to treat human patients with kahalalide compounds, in particular kahalalide F, avoiding toxicity and leading to clinical improvement.

The present invention provides a method for treating a human patient afflicted with cancer, comprising administering to said patient a therapeutically effective amount of kahalalide compound, or a pharmaceutical composition thereof. More preferably the kahalalide compound is kahalalide F.

We have found that contrary to what was expected, the dose limiting toxicity in the treatment with a kahalalide compound is liver toxicity with

grade 4 transaminase elevation. This toxicity is asymptomatic, manageable and reversible if the proper dosages and schedules are selected. Transaminases peak 4-5 hours after kahalalide infusion.

The present invention provides a pharmaceutical composition containing a recommended dose of a kahalalide compound and a pharmaceutically acceptable carrier.

In particular, the present invention provides a procedure for establishing the amount of a kahalalide compound to be recommended for dosing to patients, which procedure comprises administering the compound in a series of escalating doses to a cohort of humans, monitoring for transaminase elevation as the dose-limiting toxicity, determining a maximum tolerated dose, and establishing a recommended dose.

Such a procedure can be used in clinical trials. The maximum tolerated dose is suitably set as one in which a proportion of the cohort encounter dose-limiting toxicity. For example, the proportion is typically 2 out of 6. The recommended dose can then be established in accordance with familiar principles. Usually the recommended dose is the dose below the maximum tolerated dose, but sometimes rules are applied regarding the proportion of the cohort which encounter dose-limiting toxicity at the proposed recommended dose.

The procedure for clinical trials enables a method of preparing a ~~pharmaceutical composition containing a kahalalide compound, the method~~ comprising carrying out the procedure to establish the recommended dose, and formulating the kahalalide compound with a pharmaceutically acceptable

carrier to give a dosage form which contains the recommended dose of the kahalalide compound.

The invention further provides for the use of kahalalide compounds in the preparation of a composition for the procedures and methods of this invention.

In one aspect, the present invention provides a method for treating a human patient afflicted with cancer, comprising administering to said patient a kahalalide compound at a dose below 1200 mcg/m²/day, preferably below 930 mcg/m²/day and more preferably below 800 mcg/m²/day. Suitably the dose is at least 320 mcg/m²/day. Preferably the dose is in the range of 400-900 mcg/m²/day, preferably 500-800 mcg/m²/day, more preferably 600-750 mcg/m²/day. Especially preferred are doses of about 650-700 mcg/m²/day.

We have found that the selected schedule is important to allow for a reversion of the liver toxicity. If a daily 1 hour intravenous infusion is used during 5 days, the dose limiting toxicity is reached at 930 mcg/m²/day. Thereafter a rest period of 2 weeks is needed to reverse the toxicity effects.

Therefore in one aspect the invention provides a method for treating a human patient afflicted with cancer, comprising administering to said patient a kahalalide compound daily during 5 days at a dose below 930 mcg/m²/day, followed by a resting period of from 1 to 4 weeks in which the kahalalide compound is not administered. The dose is preferably 650-750 mcg/m²/day, more preferably about 700 mcg/m²/day. The infusion time is preferably between 1 and 24 hours, more preferably between 1 and 3 hours. Especially preferred is an infusion time of about 1 hour. The resting period

is preferably 2-3 weeks, more preferably about 2 weeks.

Surprisingly for this kind of cancer therapy, we also found that a weekly schedule is possible without resting period if the dosage is about 650 mcg/m²/day. Transaminases elevation is reversible by day 8th at about 650 but not at > 800. In this case the liver toxicity was found to be reversible within one week and no resting period is needed, with the obvious advantages this supposes.

Therefore, in another aspect the present invention provides a method for treating a human patient afflicted with cancer, comprising administering to said patient a kahalalide compound once weekly at a dose below 800 mcg/m²/day. The dose is preferably 600-700 mcg/m²/day, more preferable 650 mcg/m²/day. The infusion time is preferably between 1 and 24 hours, more preferably between 1 and 3 hours. Especially preferred is an infusion time of about 1 hour.

The above schedules and dosages allow for an effective cancer therapy in humans. We have found that kahalalide compounds, and in particular kahalalide F is effective in the treatment of advanced solid tumours (AST), including metastatic tumours. Tumours that are preferably treated are hormone independent prostate cancer, hepatocarcinoma, epithelial carcinomas, non small cell lung cancer and mesothelioma.

In a further aspect of the present invention, a medical kit for administering a kahalalide compound is provided, comprising printed instructions for administering the kahalalide compound according to the dosing schedules set forth above, and a supply of kahalalide compound in dosage units for at least one cycle, wherein each dosage unit contains the

appropriate amount of kahalalide compound for the treatments as defined above and a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION

The term "kahalalide compound" includes natural compounds, their mixtures and new compounds as defined in WO 01 58934 which is incorporated herein in its entirety by reference. Especially preferred is the compound kahalalide F.

Thus, the present invention employs a natural kahalalide such as kahalalide F or a mimic of a natural kahalalide. The mimic compounds may differ in one or more amino acids, and one or more components of the acyl side chain. Preferably they differ in one or more components of the acyl side chain. Examples of the kahalalide compound for use in this invention particularly include the compound identified as kahalalide F with a 5-methylhexyl sidechain, compounds differing only in the sidechain such as the 4-methylhexyl analogue, and mixtures thereof.

Suitably the mimics have at least one of the following features to differentiate from a parent naturally occurring kahalalide:

1 to 7, especially 1 to 3, more especially 1 or 2, most especially 1, amino acid which is not the same as an amino acid the parent compound;

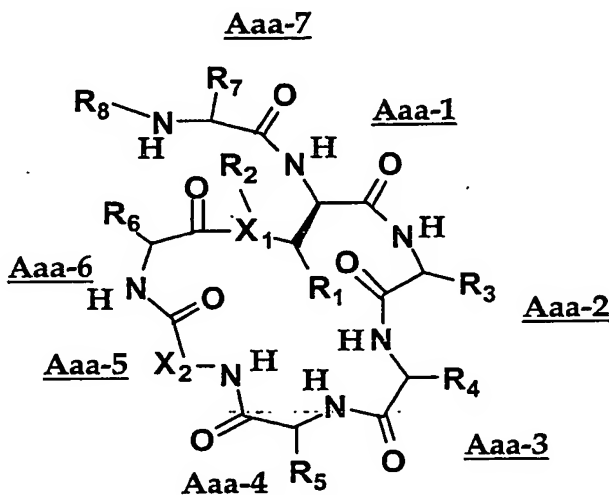
1 to 10, especially 1 to 6, more especially 1 to 3, most especially 1 or 2, additional methylene groups in the side chain acyl group of the parent compound;

1 to 10, especially 1 to 6, more especially 1 to 3, most especially 1 or 2, methylene groups omitted from the side chain acyl group of the parent compound;

1 to 6, especially 1 to 3, more especially 1 or 3, substituents added to or omitted from the side chain acyl group of the parent compound.

For cyclic kahalalides, the amino acid addition or omission can be in the cyclic ring or in the side chain.

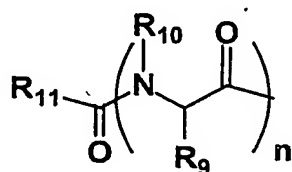
Examples of mimic comopunds are compounds related to kahalalide F, and having the formula:



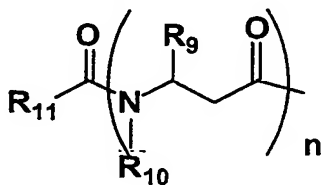
Formula II

wherein Aaa₁, Aaa₂, Aaa₃, Aaa₄, Aaa₆, and Aaa₇ are independently α-amino acids of L or D configuration, if applies; wherein R₁, R₂, R₃, R₄, R₅, R₆, R₇ are each independently H or an organic group selected from the group consisting of an alkyl group, an aryl group, an aralkyl group, and their substituted derivatives with an hydroxy group, a mercapto group, an amino group, a guanidino group, a halogen group; wherein X₁ is independently O, S, or N; wherein R₂ is, if applies, independently H or an organic group selected

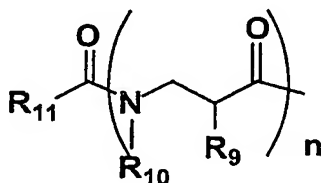
from the group consisting of an alkyl group and an aralkyl group; wherein Aaa5 is independently an amino acid of L or D configuration, if applies; wherein X₂ is independently an organic group selected from the group consisting of an alkenyl, an alkyl group, an aryl group, an aralkyl group, and their substituted derivatives with an hydroxy group, a mercapto independently H or an organic group selected from the group consisting of an alkyl group, an aryl group, an aralkyl group, and their substituted derivatives with an hydroxy group, a mercapto group, an amino group, a guanidino group, a halogen group; wherein R₈ is independently of the following formulae III, IV, or V:



Formula III



Formula IV



Formula V

wherein R₉, R₁₀, and R₁₁ are each independently H or an organic group selected from the group consisting of an alkyl group, an aryl group, an aralkyl group, and their substituted derivatives with an hydroxy group, a mercapto group, an amino group, a guanidino group, a carboxyl group, a carboxamido group, a halogen group; R₉ and R₁₀ can form part of the same

cycle; R₉ can confer S or R configuration, if applies, to the carbon attached to; and n is 0 to 6. The definitions of the amino acids can also be varied to allow for proline and analogous amino acids including hydroxyproline. The formulae (III), (IV) and (V) can be intermixed to give a side chain made up of repeat units in more than one of these formulae.

In a modification, one or more of the ring amino acids Aaa-6 and Aaa-5 of the hexaamino acid cycle is omitted or an amino acid Aaa-7 is added between Aaa-6 and Aaa-1, in order to arrive at rings having four, five or seven ring amino acids. Six ring amino acids is preferred.

Depending on the type of tumour and the developmental stage of the disease, the treatments of the invention are useful in preventing the risk of developing tumours, in promoting tumour regression, in stopping tumour growth and/or in preventing metastasis.

Administration of the compounds or compositions of the present invention is by intravenous infusion. Infusion times of up to 72 hours can be used, more preferably 1 to 24 hours, with either about 1 or about 3 hours ~~most preferred. Short infusion times which allow treatment to be carried~~ out without an overnight stay in hospital are especially desirable. However, infusion may be around 24 hours or even longer if required.

Although guidance for the dosage is given above, the correct dosage of the compound will vary according to the particular formulation, the mode of application, and the particular situs, host and tumour being treated. ~~Other~~ factors like age, body weight, sex, diet, time of administration, rate of excretion, condition of the host, drug combinations, reaction sensitivities and severity of the disease shall be taken into account. Administration can be

carried out continuously or periodically within the maximum tolerated dose.

The Recommended Dose (RD) is the highest dose which can be safely administered to a patient producing tolerable, manageable and reversible toxicity according to the Common Toxicity Criteria (CTC) established for example by the National Cancer Institute, (USA) typically with no more than 2 out of 6 patients presenting any dose limiting toxicities (DLT). Guidelines for cancer therapy frequently call for administration of chemotherapeutic agents at the highest safe dose at which toxicity is manageable in order to achieve maximum efficacy (DeVita, V. T. Jr., Hellman, S. and Rosenberg, S. A., Cancer: Principles and Practice of Oncology, 3rd ed., 1989, Lipincott, Philadelphia). For the kahalalide compounds, in particular kahalalide F, the recommended doses are as defined above and set forth in the examples.

The administration is performed in cycles, in the preferred application method, an intravenous infusion of kahalalide compounds given to the patients the first week of each cycle, the patients are allowed to recover for the remainder of the cycle. The preferred duration of each cycle is of either 1, 3 or 4 weeks; multiple cycles can be given as needed. Dose delays and/or dose reductions and schedule adjustments are performed as needed depending on individual patient tolerance of treatments, in particular dose reductions are recommended for patients with higher than normal serum levels of liver transaminases or alkaline phosphatase.

Pharmaceutical compositions of kahalalide compound that can be used include liquid (solutions, suspensions or emulsions) with suitable composition for intravenous administration, and they may contain the pure compound or in combination with any carrier or other pharmacologically active compounds. Further guidance concerning the pharmaceutical compositions

can be found in WO 02 36145 which is incorporated herein by reference in its entirety.

Thus, a combination of a non-ionic surfactant and an organic acid is suited for use with a bulking agent to give a lyophilised form of a kahalalide compound suited for reconstitution. Reconstitution is preferably effected with a mix of emulsifying solubiliser, alkanol and water.

The lyophilised composition preferably comprises mainly the bulking agent, such as at least 90 % or at least 95 % bulking agent. Examples of bulking agents are well known and include sucrose and mannitol. Other bulking agents can be employed.

The non-ionic surfactant in the lyophilised composition is preferably a sorbitan ester, more preferably a polyethylene sorbitan ester, such as a polyoxyethylene sorbitan alkanolate, especially a polyoxyethylene sorbitan mono-oleate, for example polysorbate 80. The non-ionic surfactant typically comprises a few % of the composition, such as 0 to 5 % of the composition, for instance 2 to 3 or 4 % of the composition.

The organic acid in the lyophilised composition is typically an aliphatic acid, preferably a hydroxycarboxylic acid and more preferably a hydroxypolycarboxylic acid, notably citric acid. The organic acid typically comprises a few % of the composition, such as 0 to 5 % of the composition, for instance 2 to 3 or 4 % of the composition.

The amount of kahalalide compound in the lyophilised composition is typically less than 1 %, or often less than 0.1 %, of the mix. A suitable amount is in the range 50 to 200 µg, say about 100 µg, per 100 mg of

composition.

The emulsifying solubiliser for the reconstituting agent suitably comprises an polyethylene glycol ester, notably an ester of a fatty acid, more preferably a PEG oleate such as PEG-35 oleate. The emulsifying solubiliser is suitably 0 to 10 % of the reconstituting agent, typically about 3 to 7 %, say about 5 %. The alkanol is usually ethanol, and is suitably 0 to 10 % of the reconstituting agent, typically about 3 to 7 %, say about 5 %. The remainder of the reconstituting agent is water, and gives a reconstituted solution suited for intravenous injection.

Further dilution of the reconstituted solution with 0.9 % saline may be appropriate for infusion of the kahalalide compound.

In a particularly preferred embodiment, the lyophilised composition comprises 150 µg kahalalide F; 150 mg sucrose; 3 mg anhydrous citric acid; and 3 mg of polysorbate 80.

The preferred reconstituting agent then comprises 2 to 7 %, say about 5 %, emulsifying solubiliser; 2 to 7 %, say about 5 %, alcohol; and remainder water.

The invention additionally provides kits comprising separate containers containing the lyophilised composition and the reconstituting agent. Methods of reconstitution are also provided.

The present invention further provides a method of treating any mammal, notably a human, affected by cancer which comprises administering to the affected individual a therapeutically effective amount of a

pharmaceutical composition thereof prepared by reconstitution of a lyophilised composition of this invention. The present invention can be employed particularly for treatment of patients with refractory cancers that do not respond favourably to other treatments. In particular, the compositions of this invention can be employed after other chemotherapy has been tried and not worked.

In one embodiment, the reconstituted solution is prepared for infusion and is administered in a 3-hour infusion on concentrations of up to around 20 or 25 $\mu\text{g/ml}$, typically up to 15 $\mu\text{g/ml}$. Suitable infusion equipment preferably includes a glass container, rather than one of polyethylene. Tubing is preferably of silicone.

We prefer that infusion times of up to 24 hours are used, and as explained we prefer an infusion time of about 1 hour. In a variation, the infusion time is 2-12 hours, such as 2-6 hours. Short infusion times which allow treatment to be carried out without an overnight stay in hospital are especially desirable. However, infusion may be 12 to 24 hours or even longer if required. Infusion may be carried out at suitable intervals of say 2 to 4 weeks. In an alternative dosing protocol, the kahalalide compound such as kahalalide F is administered for say about 1 hour for 5 consecutive days every 3 weeks. Other protocols can be devised as variations.

The compounds and compositions of this invention may be used with other drugs to provide a combination therapy. The other drugs may form part of the same composition, or be provided as a separate composition for administration at the same time or a different time. The identity of the other drug is not particularly limited.

EXAMPLES OF THE INVENTION

Clinical trials were carried out based on the following protocols:

Number of patients per dose level and Dose escalation

The rate of subject entry and escalation to the next dose level will depend upon assessment of the safety profile of patients entered at each dose level. Toxicity will be evaluated and graded according to the Common Toxicity Criteria, version 2.0.

In order to minimize the number of patients treated at the subtoxic dose levels, a single patient will be treated per dose level with 100% dose escalation in the absence of any toxicity G2 (excluding alopecia) during their first course of treatment. After the occurrence of grade 2 toxicity (excluding asthenia, alopecia, nausea and vomiting or anemia), the dose level is expanded to three patients with only 50% incremental increase in dosage in advancing to the next dose level. For the occurrence of grade 3 non-hematological toxic effects the dose level should be expanded up to six patients. This second cohort of 3 patients will be included consecutively. If the first or second patient develops dose limiting toxicities no further patients will be treated at this dose level, it will be defined as MTD and the accrual will begin at a lower dose level. If only one DLT occurs at this dose level another 3 patients will be included at the next dose level with an increase of 25% only.

Observed toxicities	Action
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<G1 toxicities	Treat 1 patient per dose level with 100% dose escalation
G2 toxicities	Treat 3 pats at that dose level with 50% increase in Dose escalation
G3 toxicities non-hematological	Expand current dose level up to 6 pats and 25% increase in dose escalation
$\geq 1/3$ or $\geq 2/6$ DLTs	MTD

Clinical pharmacokinetic data on Kahalalide F will become available during the course of each dose level and will be considered when making a final judgement.

There is no inpatient dose escalation, only de-escalation. If the toxicity is grade 3 or worse in a course of chemotherapy, then the dose is reduced one level for the next course.

Maximum Tolerated Dose (MTD) and Recommended Dose (RD) for Phase II studies

The maximum tolerated dose (MTD) is defined as the dose at which at least 2 out of 3 or more than 3 patients experience DLT. However, it is possible that additional patients may experience DLT due to the timing of patient enrollment into that dose level.

Once an MTD level is established, subsequent patients should be treated at the next lower dose level. Intermediate doses may be used in some instances and flexibility is an integral part of the protocol.

At the RD, sufficient number of patients will be accrued to further define the toxicity profile at this dose level.

KHF A 001-00

Definition of Dose Limiting Toxicities

Dose limiting toxicities (DLTs) are defined as follows:

Grade IV Neutropenia lasting for ≥ 5 days or with a temperature > 38.5 .

Grade IV thrombocytopenia.

Any other grade III or IV non hematological toxicity, excluding nausea, emesis and hypersensitivity reactions.

Grade III or IV liver toxicity if not reversible by day 21.

These toxicities are only considered DLTs if they happen during cycle 1.

KHF 002-01

Definition of Dose Limiting Toxicities

The toxicity will be evaluated and classified in grades according to the Common Toxicity Criteria (CTC) version NCI 2.0, March 1998.

Dose limiting toxicities (DLTs) are defined as follows:

ANC $< 500/\text{mm}^3$ for more than 5 days.

ANC $< 500/\text{mm}^3$ with a temperature of 38.5 or more.

Plaquetas $< 25000/\text{mm}^3$

Any other non-hematological grade 3-4 toxicity excluding:

nausea, emesis without prophylaxis

G3 transaminases increase >14 days

Hypersensitivity reactions

Example 1

Preliminary Report

Phase I and Pharmacokinetic Study of Kahalalide F in Patients With Advanced Androgen Refractory Prostate Cancer

INTRODUCTION: Kahalalide F (KF) is one of a family of novel dehydroaminobutyric acid-containing peptides isolated from the Hawaiian herbivorous marine species of mollusk, *Elysia rufescens*. KF displays both in vitro and in vivo anti-tumour activity in various solid tumour models including breast, colon, non-small cell lung, and in particular prostate cancer. On the basis of its selectivity, KF is now further developed as a potential anticancer agent against androgen independent prostate tumours.

OBJECTIVE: In the present phase I clinical and pharmacokinetic (PK) study the toxicity profiles PK and anti-tumour activity of KF are investigated.

METHODS: KF is administered as an intravenous infusion over one hour, during five consecutive days every three weeks in patients with advanced or metastatic androgen refractory prostate cancer. On the basis of the MTD

values defined in mice, a starting dose of 20 $\mu\text{g}/\text{m}^2/\text{day}$ was selected, which is equivalent to a total dose of 100 $\mu\text{g}/\text{m}^2$. PK of KF were determined in plasma during the first course. Bioanalysis of KF was performed by LC-MS/MS. LDH, AF and especially PSA levels of each patient were also

evaluated during the study to determine the activity of KF. RESULTS AND DISCUSSION: At present 7 patients have been registered. Patients had a median age of 66 years (range 54-75). One patient per level was entered at 20, 40, 80 and 160 $\mu\text{g}/\text{m}^2/\text{day}$. Due to transaminase elevation a number of 4 patients were entered at the current dose level, 320 $\mu\text{g}/\text{m}^2/\text{day}$. The first patient of this study was re-entered at this dose level. Observed adverse events were rapidly reversible mild headache, fatigue, pain and local edema. The only drug related toxicity to date was a rapidly reversible CTC grade 3 ASAT that occurred at 320 $\mu\text{g}/\text{m}^2/\text{day}$. PK revealed a linear relationship between dose and AUC over the whole dose range. Total plasma clearance was 267 mL/min (± 115) and the terminal half-life of intravenous KF in these patients was 0.46 h (± 0.13). Maximum plasma concentrations reached at the current dose level (35-50 ng/mL) are potentially active for prostate cancer in the clonogenic tumour assay (activity from 15 ng/mL). Thus far, the schedule is well tolerated. One patient showed a significant decrease in PSA level (>50%) associated to clinical improvement (pain relief). Two additional patients experienced minor PSA reductions, one still ongoing after two cycles. The maximum tolerated dose has not been reached yet and the study is ongoing.

Example 2

KHF-A-001-00. Phase I Clinical and Pharmacokinetic study to determine the safety of kahalalide F administered as a daily x 5 over 1 hour Infusion every 21 days in patients with advanced or metastatic prostate cancer.

The first clinical trial with KHF is being run in The Netherlands. It is addressed to prostate cancer patients according to the high selectivity

exhibited in the preclinical programme. The toxicity data in rodents and dogs shows the feasibility to give daily doses equivalent to the single dose MTD in a repeated fashion (daily times five): such schedule may significantly enhance the therapeutic profile of KF in patients bearing hormone resistant prostate cancer.

A dose of 20 mcg/m² was considered a safe starting dose on the basis of acute toxicity studies in animals. The trial was designed as an accelerated dose escalation (pharmacokinetically guided).

One patient (the first one treated in this trial) received 4 cycles at the first dose level. 2 months after stopping the treatment, was included at the current dose level (V) and received another 4 cycles. Grade 3 hypertransaminasemia was the reason to expand the cohort in the 5th level.

Level	I	II	III	IV	V	VI
Dose	20	40	80	160	320	425
Increase%		100	100	100	100	33
Patient	1	1	1	1	5	3
Cycles	4	1	8	4	2,4,8,2,2	3, 2, 2
Worst toxicity	none	none	none	none	G3 Hypertrans	none
Efficacy			PR	SD		

Level	VII	VIII	IX	X
Dose	560	700	930	700
Increase%	33	25	33	
Patient	3	3	3	2
Cycles	4, 2, 2	2,2,2	5, 3, 2	

Worst	G3	none	G4
toxicity	Hypertrans		Hypertrans
			Hypersensitivity
Efficacy	SD		

20 patients and 66 cycles could be evaluated by August, 2002.

HEMATOLOGIC TOXICITY % (worst per patient)

19 patients	Grade 1	Grade 2	Grade 3	Grade 4
Neutrophils	5	5	0	0
Leukocytes	10.5	0	0	0
Platelets	21.1	0	0	0
Hemoglobin	63.2	26.3	0	0

NON-HEMATOLOGIC TOXICITY % LAB ABNORMALITIES per patient

20 patients	Grade 1	Grade 2	Grade 3	Grade 4
Creatinine	35	0	0	0
Bilirubin	10	0	0	0
Alk.phosphatase	35	20	25	5
GOT	40	15	15	10
GPT	15	25	20	10
GGT	35	15	25	5
HypoNa+	10	0	5	5
HypoK+	20	0	0	0
HypoCa*	65	0	0	0
Hypo P	10	15	0	0
Albumin	30	10	5	0
CPK	35	0	0	0

*Calcium adjusted

Most frequently reported NON-HEMATOLOGIC TOXICITIES

20 patients	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	10	5	0	0
Fatigue	35	10	25	0
Nausea	15	10	0	0
Hypersensitivity	20	5	0	0
Hypertension	0	0	15	0
Inject-site reaction	10	20	0	0
Periph-sens neuro	20	0	5	0
Vomiting	15	10	0	0

From preclinical studies renal and neurologic were the most expected toxicities, but surprisingly none of them has constituted remarkable toxicity. However, liver toxicity was the most commonly seen as grade 4 transaminases elevation in the MTD (GOP, GPT levels). Patients also complain of puncture or prick on hands palms during the infusion.

Hypertension and alkaline phosphatase were not drug-related.

As it was predicted by preclinical experiments no hematological toxicity was seen. No grade 3-4 emesis was reported.

Regarding efficacy, one patient was evaluated as a partial response (evaluated by PSA). This patient received 8 cycles. Two more patients exhibited SD (they were also evaluated by PSA) as best response and received 4 cycles. All these patients concomitantly showed clinical

improvement.

Example 3

KHF-A-002-01. Phase I Clinical and Pharmacokinetic study to determine the safety of Kahalalide F administered as a weekly infusion over 1 hour in patients with solid tumours.

This trial was addressed to any solid tumours and was designed as a classical escalation. The starting dose was higher because we had some information from the first trial, and this allowed us to skip the first steps. One cycle in this trial means a week, so 4 cycles mean 1 month of treatment.

The second dose level (400) was expanded because of two unrelated adverse events: grade 3 diarrhea and death due to gastrointestinal bleeding. This was also the reason why the next escalation was only 32.5% instead of 50%. No toxicities were reported in this level and the following escalation was 50% again.

The DLT was identified at 1200 mcg/m², and was grade 4. hypertransaminasemia non reversible by day 21. The time of onset was located at 5 hours after the infusion. This was not a scheduled determination and that was why the dose was descalated looking for previously unidentified grade 4 hypertransaminasemia. The 4th level was reexplored and this second time, grade 4 hypertransaminasemia was identified as DLT again at this dose level.

19 patients and 145 cycles were evaluated.

Level	I	II	III	IV	V
Dose	266	400	530	800	1200
Increase%					
Patient	3	6	3	3	5
Cycles	5,8,8	2,6,7, 9,21,4	7,8,16	10,11,8	8,8,3,8
Worst toxicity	-				Hypersensitivity hypertrans
Efficacy	-	Cavum Hepatocell	NSCLC		

Level	VI	VII	VIII
Dose	1000	800	650
Increase%			
Patient	3	3	10
Cycles	3,1,3	2,1,1	
Worst toxicity	Hypersensitivity hypertrans	G4 Hypertrans	
Efficacy			

Patients have complained of puncture or prick on hands palms in all the dose levels.

One SAE with hypersensitivity reactions was reported. The patient had both pruritus and bronchoconstriction after the first cycle at 1200 mcg/sm. He could not be retreated in spite of administering standard premedication.

OTHER TOXICITIES

HEMATOLOGIC TOXICITY (worst per patient)

	Grade 1	Grade 2	Grade 3	Grade 4
Neutrophils	5.3	5.3	0	0
Leukocytes	15.8	5.3	0	0
Platelets	10.5	0	0	0
Hemoglobin	57.9	21.1	0	0

NONHEMATOLOGIC TOXICITY. LABORATORY ABNORMALITIES

	Grade 1	Grade 2	Grade 3	Grade 4
Creatinine	31.6	5.3	0	0
Bilirubin	5.6	0	0	0
Alk.phosphatase	27.8	11.1	0	0
GOT	38.9	0	0	16.7
GPT	22.2	5.6	0	16.7
GGT	16.7	11.1	5.6	11.1
Na+ hypo	21.1	0	0	5.3
K+ hypo	5.3	0	0	0
Ca++ hypo	21.1	0	0	0
Ca++ hyper	84.2	0	0	0
CPK	36.8	0	0	0

Most frequently reported NON-HEMATOLOGIC TOXICITIES

20 patients	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	0	5.3	5.3	0
Fatigue	21.1	21.1	0	0

		28		
Nausea	31.6	10.5	0	0
Hypersensitivity	15.8	5.3	5.3	0
Hypertension	0	0	0	0
Inject-site	0	5.3	0	0
reaction				
Periph-sens	36.8	0	5.3	0
neuro				
Vomiting	10.5	5.3	0	0

EFFICACY

Some hints of efficacy were seen in this trial, in a patient with a epidermoid carcinoma of the cavum, treated at 400 mcg/m². Subjective improvement and non evaluable response (ORL exploration). Another patient with hepatocellular carcinoma, treated at 400 mcg/m². He received the treatment during 6 months (24 cycles). Partial response in one target lesion (overall response: stable disease). Also in a patient with non small cell lung cancer, treated at 530 mcg/m². He received the treatment during 4 months (16 infusions) without evidence of progression disease. One patient with peritoneal mesothelioma had clinical benefit with reduction of ascytes volume.

HEMATOLOGIC TOXICITY

KHF was supposed to be a non myelosuppressor agent. This prediction seems to have been confirmed in the clinical programme. Grade 1-2 neutropenia was seen in 10% of patients. No grade 3-4 toxicities were

reported.

RENAL TOXICITY

This was an expected toxicity for KHF since it was dose limiting toxicity in the preclinical programme. However renal toxicity has not been a relevant toxicity. Only about 35% of patients exhibited grade 1 renal toxicity. Since this renal toxicity was expected to be more tubular than glomerular, we have carefully reviewed seric ions. Grade 1 hypokalemia occurred in the 20 % of patients, grade 1 and 2 hypophosphatemia in 10 and 15%. Grade 1 hypocalcemia was a frequent feature in the first trial (patients with prostate cancer) but it was not so frequent in patients treated in the second trial. Ions loss in urine should be confirmed.

HYPERTRANSAMINASEMIA

It has been the DLT for KHF. It is clearly dose-related. At 800-1200 mcg/m²/wk all the patients had grade 4 hypertransaminasemia. Hypertransaminasemia peaks 4-5 hours after the infusion of KHF and is not reversible by day 8 for patients treated at 1000 and 1200. One patient showed LDH elevation too. Neither bilirubin nor alkaline phosphatase elevations were reported. Patients remained asymptomatic. This toxicity was completely reversible.

Though transaminases are found in other organs, a grade 4 ALT is a marker of hepatocellular injury.

HIPERSENSITIVITY

Probably the most frequent toxicity observed with KHF is the palm hand prick referred by patients while the infusion. Sometimes this complaint was accompanied by other symptoms like erythema or pruritus in other locations.

Bronchoconstriction was observed in two patients at the highest dose level (1000 and 1200). Pruritus with redness and sometimes facial edema was seen. It could be more a toxic effect than a immune mediated (hypersensitivity reaction) sine it was more commonly reported in the highest levels.

CONCLUSIONS

In this second example dose limiting toxicity for Kahalalide F was grade 4 hypertransaminasemia as in the previous example with a different schedule. It is an asymptomatic and reversible feature that appears 4-5 hours after the infusion of KHF. Hypersensitivity reactions with cutaneous features were commonly reported at highest levels.

Lack of hematologic toxicity was confirmed as it was predicted by preclinical studies.

CLAIMS

1. A pharmaceutical composition containing a recommended dose of a kahalalide compound and a pharmaceutically acceptable carrier.
2. A procedure for establishing the amount of a kahalalide compound to be recommended for dosing to patients, which procedure comprises administering the compound in a series of escalating doses to humans, monitoring for transaminase elevation as the dose-limiting toxicity, determining a maximum tolerated dose, and establishing a recommended dose.
3. A method of preparing a pharmaceutical composition containing a kahalalide compound, the method comprising carrying out the procedure according to claim 2 to establish the recommended dose, and formulating the kahalalide compound with a pharmaceutically acceptable carrier to give a dosage form which contains the recommended dose of the kahalalide compound.
4. A composition of a kahalalide compound containing a recommended dose determined by a procedure according to claim 2.
5. The use of a kahalalide compound in the preparation of a composition for a procedure according to claim 2.

6. The use of a kahalalide compound in the preparation of a medicament for use in a method of therapy of cancer in a human patient, the medicament containing a recommended dose of the kahalalide compound.
7. The use of claim 6, wherein the recommended dose is established by a procedure according to claim 2.
8. A composition according to claim 1 or 4, or a procedure according to claim 2, or a method according to claim 3, or a use according to claim 6 or 7, wherein the recommended dose is less than the amount of the kahalalide compound which causes a grade 4 transaminase elevation.

9. A composition according to claim 1, 4 or 8, which comprises a lyophilised mix of a kahalide compound, a non-ionic surfactant, an organic acid and a bulking agent.

10. A kit comprising a formulation of claim 9, together with instructions for dilution with a reconstitution solution of a mix of emulsifying solubiliser, alkanol and water.

11. A method of treating a human with a kahalalide compound which comprises administering at least 320 mcg/m²/day.
12. A method according to claim 11, for treating a human patient afflicted with cancer, comprising administering to said patient a kahalalide compound at a dose below 1200 mcg/m²/day.
13. A method according to claim 12, wherein the dose is below 930 mcg/m²/day.
14. A method according to claim 12, wherein the dose is below 800 mcg/m²/day.
15. A method according to claim 11, wherein the dose is in the range of 400-900 mcg/m²/day.
16. A method according to claim 15, wherein the dose is 500-800 mcg/m²/day.
17. A method according to claim 15, wherein the dose is 600-750 mcg/m²/day.

18. A method of administering a kahalalide compound to a human, wherein the compound is administered according to a schedule which is selected to allow for a reversion of liver toxicity.
 19. A method for treating a human patient afflicted with cancer, comprising administering to said patient a kahalalide compound daily during 5 days at a dose below 930 mcg/m²/day, followed by a resting period of from 1 to 4 weeks in which the kahalalide compound is not administered.
 20. A method according to claim 19, wherein the dose is 650-750 mcg/m²/day.
 21. A method according to claim 19, wherein the dose is about 700 mcg/m²/day.
-
22. A method according to claim 19, 20 or 21, wherein the infusion time is 1 to 24 hours.
 23. A method according to claim 22, wherein the infusion time is 1 to 3 hours.
-

4. A method according to claim 23, wherein the infusion time is about 1 hour.
25. A method according to any of claims 19 to 24, wherein the resting period is 2-3 weeks.
26. A method according to claim 25, wherein the resting time is about 2 weeks.
27. A method for treating a human patient afflicted with cancer, comprising administering to said patient a kahalalide compound once weekly at a dose below 800 mcg/m²/day.
28. A method according to claim 27, wherein the dose is 600-700 mcg/m²/day.
29. A method according to claim 28, wherein the dose is 650 mcg/m²/day.
30. A method according to claim 27, 28 or 29, wherein the infusion time is 1 to 24 hours.

31. A method according to claim 30, wherein the infusion time is 1 to 3 hours.

32. A method according to claim 31, wherein the infusion time is about 1 hour.

33. A method according to any of claims 11 to 32, wherein the kahalalide compound is kahalalide F.

34. A method according to any of claims 11 to 33, wherein the human has a metastatic or other advanced solid tumour.

35. A method according to any of claims 11 to 34, wherein the human has a hormone independent prostate cancer, hepatocarcinoma, epithelial carcinoma, non small cell lung cancer or mesothelioma.

36. The use of a kahalalide compound in the preparation of a medicament for a method according to any of claims 11 to 35.

ABSTRACT

Procedures for clinical trials of kahalalide compounds are provided, leading to new formulations of kahalalide compounds.

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